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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	PAPER NUMBER
1635	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/540,843	Applicant(s) GILCHREST ET AL.	
	Examiner Brian Whiteman	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-92 is/are pending in the application.

4a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-11,13-17,19-29,31,32,51,52,57,58,63,64,69,71-83,85,86,88 and 89 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 31 March 2000 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6, 11
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: 11 .

Continuation of Disposition of Claims: Claims withdrawn from consideration are 12,18,24,30,33-50,53-56,59-62,65-68,70,84,87 and 90-92.

DETAILED ACTION

Non-Final Rejection

Claims 1-11, 13-17, 19-23, 25-29, 31-32, 51-52, 57-58, 63-64, 69, 71-83, 85-86, and 88-89 are pending examination.

Priority

Priority to the instant application being a CIP of 09/048,927 filed on 3/26/98, CIP of 08/952,697 filed on 11/30/98, and CIP of 08/467,012 filed on 6/6/95 is acknowledged.

Information Disclosure Statement

The information disclosure statement filed on December 20, 2000 does not fully comply with the requirements of 37 CFR 1.98 because: applicant does not properly cite a journal article listed on the 1449. The volume number of article AY2 is incorrect.

References have been considered by the examiner, but in order to have article AY2 initialed and dated on the 1449, a new 1449 properly citing the journal article must be filed with the response to this office action. Failure to comply with this notice will result in the above mentioned information disclosure statement being placed in the application file with the non-complying information **not** being considered. See 37 CFR 1.97(i).

Specification

The specification contains a misspelling of the word "dinucleotide" on page 10, line 18. These and any other, spelling errors should be corrected in response to this office action. Applicant is encouraged to review the specification for additional spelling errors.

Claim Objections

Claims 1, 2, 57, 58, and 69 are objected to because of the following informalities: Claim 1 reads on non-elected species. SEQ ID NO: 3 and 7 listed in claims 2, 57, 58, and 69 are the exact same sequence as stated by the applicants in paper no. 10, page 2 and duplicate sequences cannot be claimed in the same application. Appropriate correction is required.

The addition of new claims 71-92 and the amendment of the specification in paper no. 4 filed on 9/22/00 is acknowledged with no new matter being added.

Reply to restriction requirement

In response to restriction in paper no. 7, dated 7/3/01, applicants elected group I (claims 1-32, 51-70, 71-83, 85-89, and 90-92) and phosphodiester for species of backbone in paper no. 8, filed 8/8/01.

Applicant's election of Group I and phosphodiester as species in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

However upon further review another election/restriction (dated 9/20/01) due to an undue burden on the examiner to search because of the twelve distinct oligonucleotide sequences being claimed in the instant application.

In response to election of species in paper no. 9 filed on 9/20/01, applicants elected SEQ ID NO: 5 as the species in paper no 10 filed on 12/31/01 with traverse. Applicant's election with traverse of species (SEQ ID NO: 5) in Paper No. 10 is acknowledged. The traversal is on the

ground(s) that: 1) Except for SEQ ID NOs: 2, 8, and 10, the oligonucleotides represented by SEQ ID NOs: 1-12 are related, 2) The Commissioner determined that normally, ten nucleotide sequences constitute a reasonable number for examination purposes. See page 2.

This is found partially persuasive because SEQ ID NO: 9 is the complement of SEQ ID NO: 5 and SEQ ID NO: 11 is a portion of SEQ ID NO: 5 and SEQ ID NO: 12 is a portion of SEQ ID NO: 9. However, the remaining sequences are distinct and the remaining nucleotide sequences are distinct because the nucleotide sequences do not appear to share a common structure. In addition, it was determined that, "**up to 10 independent** and distinct nucleotide sequence will be examined in a single application without restriction, 1232 OG 242 (March 21, 2000)." Therefore, it would be an undue burden on the examiner to search all the nucleotide sequences, since each oligonucleotide sequence is distinct and from a different species and the USPTO resources are stretched to the limit.

The requirement is still deemed proper and is therefore made FINAL.

Furthermore, after a search of the art, the methods listed in the claimed invention comprising SEQ ID NOs 5 are novel and a further search discovered that SEQ ID NO: 7 is not novel for the methods listed in the claimed invention because SEQ ID NO: 7 is the same sequence as set forth in SEQ ID NO: 3. Therefore, SEQ ID NO: 7 will be added to the elected species, however the other SEQ ID NOs are still considered part of the non-elected species.

Claims 12, 18, 24, 30, 33-50, 53-56, 59-62, 65-68, 70, 84, 87, and 90-92 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention and non-elected species of backbones and non-elected sequences [SEQ ID NOs: 1-2, 4, 6, 8, and 10 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being

drawn to a non-elected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

Claims 1-11, 13-17, 19-23, 25-29, 31-32, 51-52, 57-58, 63-64, 69, 71-83, and 85-86 and 88-89 are pending examination.

Double Patenting

The non-statutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper time-wise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 6, 14-16, 19, 57-58, 69, 75, 83, and 88 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over either claims 2, 3, and 5 of U.S. Patent No. 6,147,056.

Claim 2 of patent '056 is directed to a method of treating vitiligo in a mammal, comprising administering topically to the epidermis of the mammal an effective amount of DNA fragments selected from the group consisting of: SEQ ID NOs: 1, 2, 3, and 4 combinations thereof. Furthermore, claim 3 of patent '056 is drawn to a method of reducing photoaging in a mammal, comprising administering topically to the epidermis of the mammal an effective amount of DNA fragment selected from the group consisting of SEQ ID NOs: 1, 2, 3, and 4 combinations thereof. In addition, claim 5 from patent '056 is directed to a method of treating

hyperproliferative disorder, affecting skin cells in a mammal, comprising administering the skin cells of interest in the mammal an effective amount of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4 and combination thereof.

The differences between claim 2 of patent '056 and claims 14-16 of the pending application is that the instant application uses the phrase "treating vitiligo in a mammal". However, one of ordinary skill in the art would have known that treating vitiligo and increasing melanin production in epidermal cells are obvious variants of one another because vitiligo results from a mammal losing their melanocytes.

The differences between claim 5 of patent '056 and claim 75 of the pending application is that the instant application uses the phrase "epithelial cells". However, one of ordinary skill in the art would have known that a skin cell is a species of an epithelial cell. In addition, the different between claim 5 of patent '056 and claim 88 of the pending application is that the instant application uses the phrase "treating malignant cells of a mammal". However, one skilled in the art would understand that the term "hyperproliferative disorder" would obviously encompass treating malignant cell as well as non-malignant cell populations, which appear to differ from the surrounding tissue both morphologically and genotypically.

Furthermore, the difference between the claim 3 of patent '056 and claims 1-4, and 6 of the pending application is that the instant application further comprises the phrase, "the oligonucleotide comprise of a phosphodiester backbone". However, one of ordinary skill in the art would have known that an oligonucleotide in its natural state would possess a phosphodiester backbone; therefore, it would have been inherent for the oligonucleotides in the claimed invention to have a phosphodiester backbone. Furthermore, in order for the oligonucleotides to

be used in the methods of patent '056, it would have to be in placed in a physiological acceptable carrier. Thus, claims 6, 57-58, 69 are obvious variants of the claims in patent '056.

Therefore, the claims of the instant application and patent '056 are obvious variants of one another.

Claims 1, 3-4, 6, and 85-86 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11-14 and 20-25 of US Patent No. 5,955,059.

Claims 11-14 of patent '059 are drawn to a method of reducing photoaging in a mammal, comprising administering topically to the epidermis of the mammal an effective amount of DNA fragments that are approximately 2-200 bases in length, the DNA fragments being selected from the group consisting of single-stranded DNA fragments, double-stranded DNA fragments, and a mixture of single- and double stranded fragments. Furthermore, claims 20-24 are drawn to a method of inhibiting UV-induced dermatoses in a mammal, comprising topically administering to the epidermis epithelial cells of interest in the mammal an effective amount of DNA fragments that are approximately 2-200 bases in length, the DNA fragments being selected from the group consisting of: single stranded DNA fragments, double stranded DNA fragments, and a mixture of single and double stranded DNA fragments. Furthermore, claim 25 is drawn to a method of reducing the susceptibility to skin cancer in a mammal, comprising topically administering to the epidermis epithelial cells of interest in the mammal an effective amount of DNA fragments that are approximately 2-200 bases in length, the DNA fragments being selected from the group

consisting of: single stranded DNA fragments, double stranded DNA fragments, and a mixture of single and double stranded DNA fragments.

The differences between the claims 11-14 of patent '059 and the claims 1, 3-4, and 6 of the pending application are that the instant application further comprises that the oligonucleotide comprise of a phosphodiester backbone. However, one of ordinary skill in the art would have known that an oligonucleotide in its natural state would possess a phosphodiester backbone and it would have been inherent for the oligonucleotides in the claimed invention to have a phosphodiester backbone. Furthermore, in order for the oligonucleotides to be used in the methods of patent '059, it would have to be in placed in a physiological acceptable carrier or a delivery vehicle.

The differences between the claims 20-24 of patent '059 and claim 86 of the pending application are that the instant application is drawn to a method of preventing or reducing DNA damage in a cell, wherein said DNA damage is caused by UV irradiation, comprising contacting said cell with an effect amount of DNA fragments. However, one of ordinary skill in the art would have known that the phrase "reducing DNA damage in a cell, wherein said DNA damage is caused by UV irradiation" in the instant application and the phrase "inhibiting UV-induced dermatoses in a mammal" are obvious variants of each other because both phrases encompasses inhibiting DNA damage caused by UV irradiation.

The differences between the claim 25 of patent '059 and claim 85 of the pending application are that the instant application is drawn to a method of preventing or reducing DNA damage in a cell, wherein said DNA damage is caused by UV irradiation, comprising contacting said cell with an effect amount of DNA fragments. However, one of ordinary skill in the art

would have known that the phrase "inhibiting proliferation of skin cells in a mammal" in the instant application and the phrase "reducing the susceptibility to skin cancer in a mammal" are obvious variants of each other because both phrases encompass inhibiting the proliferation of skin cells in a mammal.

Therefore, the claims of the instant application and claims of the patent '059 are obvious variants of one another.

Claims 1, 5, 14, and 17 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2 and 3 of U.S. Patent No. 6,147,056 in view of Iversen et al. (US Patent No. 5,643,890, IDS).

Claim 2 of patent '056 is directed to a method of treating vitiligo in a mammal, comprising administering topically to the epidermis of the mammal an effective amount of DNA fragments selected from the group consisting of: SEQ ID NOs: 1, 2, 3, and 4 combinations thereof. Claim 3 from patent '056 is directed to a method of reducing photoaging in a mammal, comprising administering topically the epidermis of the mammal an effective amount of DNA fragment selected from the groups consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4 and combination thereof.

The differences between claims 2 and 3 of patent '056 and claims 1, 5, 14, and 17 of the pending application is that the instant application further uses the DNA fragments at a concentration of about 1uM to about 500uM. However, Iversen teaches that oligonucleotides can be administered at a concentration of 1uM to 6uM (column 6 and Figure 10). Thus, one of ordinary skill in the art would have been motivated to combine the teaching provided by

patent'056 in view Iversen to use an oligonucleotide at a concentration of 1uM to 6uM in a method of reducing photoaging in a mammal of increasing melanin production in epidermal epithelial skin cells. One of ordinary skill in the art would have expected, absent evidence to the contrary, that the concentration taught by Iversen would produce an equivocal additive effect that would lead to reducing photoaging in a mammal.

Therefore, the claims of the instant application and the patent '056 in view of West et al. (US Patent No. 6,194,206) are obvious variants of one another.

Claims 75 and 77-78 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 5 of U.S. Patent No. 6,147,056 in view of applicants' own admission that liposomes such as those described in US Patent No. 5,077,211 of Yarosh can be used (page 14, lines 13-17).

Claim 5 from patent '056 is directed to a method of treating hyperproliferative disorder, affecting skin cells in a mammal, comprising administering the skin cells of interest in the mammal an effective amount of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4 and combination thereof.

The differences between claim 5 of patent '056 and the pending application is that the instant application further uses a liposome comprising the DNA fragments. However, applicants' own admission that liposomes such as those described in US Patent No. 5,077,211 of Yarosh can be used (page 14, lines 13-17). Thus, one of ordinary skill in the art would have been motivated to combine the teaching provided by patent'056 in view of applicants' own admission to produce a gene delivery vehicle comprising a DNA fragment in a method of

treating hyperproliferative disease affecting epidermis epithelial cells in a mammal. One of ordinary skill in the art would have expected that the combination of the liposome and a DNA fragment would produce an equivocal additive effect that would lead to treating a hyperproliferative disease affecting epidermis epithelial cells in a mammal.

Therefore, the claims of the instant application and the patent '056 in view of applicants' own admission on page 14 are obvious variants of one another.

Claims 75 and 77-79 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 5 of U.S. Patent No. 6,147,056 in view of West et al. (US Patent No. 6,194,206).

Claim 5 from patent '056 is directed to a method of treating hyperproliferative disorder, affecting skin cells in a mammal, comprising administering the skin cells of interest in the mammal an effective amount of DNA fragment selected from the groups consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4 and combination thereof.

The differences between claim 5 of patent '056 and the pending application is that the instant application further uses a propylene glycol comprising the DNA fragments. However, West teaches that propylene glycol or encapsulation in liposomes can be used in the administration of a DNA fragment (column 38, line 65- column 40, line 4). Thus, one of ordinary skill in the art would have been motivated to combine the teaching provided by patent'056 in view West to produce a gene delivery vehicle comprising a DNA fragment in a method of treating hyperproliferative disease affecting epidermis epithelial cells in a mammal. One of ordinary skill in the art would have expected that the combination of either propylene

glycol or liposomes and a DNA fragment would produce an equivocal additive effect that would lead to treating a hyperproliferative disease affecting epidermis epithelial cells in a mammal.

Therefore, the claims of the instant application and the patent '056 in view of West et al. (US Patent No. 6,194,206) are obvious variants of one another.

Claims 85 and 89 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 5 of U.S. Patent No. 6,147,056 in view of Beer-Romero et al. (US Patent No. 5,858,987).

Claim 5 from patent '056 is directed to a method of treating hyperproliferative disorder, affecting skin cells in a mammal, comprising administering the skin cells of interest in the mammal an effective amount of DNA fragment selected from the groups consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4 and combination thereof.

The differences between claim 5 of patent '056 and the pending application is that the instant application further states that the DNA fragment is topically administered to said cells of the mammal. However, Beer-Romero teaches topical administration of a DNA fragment to epithelial cells (column 32, claim 18). Thus, one of ordinary skill in the art would have been motivated to combine the teaching provided by patent'056 in view Beer-Romero to topically administer a DNA fragment to epithelial cells in a mammal because of the routine practice of delivering DNA fragment to skin cells of a mammal. One of ordinary skill in the art would have expected that the topical administration would produce an equivocal additive effect that would lead to inhibiting proliferation of skin cells in a mammal.

Therefore, the claims of the instant application and the patent '056 in view of Beer-Romero et al. (US Patent No. 5,858,987) are obvious variants of one another.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 9-11, and 13 as best understood, are readable on a genus of a mimic of telomere disruption, wherein the genus of a mimic of telomere disruption is not claimed in a specific biochemical or molecular structures that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates a genus of a mimic of telomere disruption. The as-filed specification provides sufficient description of a species of a telomere DNA sequence from the 3' telomere overhang (page 7, SEQ ID NO: 5).

However, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of a mimic of telomere disruption as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative

number of species of biochemical or molecular structures of a mimic of telomere disruption that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to support the present claimed invention directed to a genus of a mimic of telomere disruption. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming mimic of telomere disruption, wherein said mimic comprises at least one oligonucleotide that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of a mimic of telomere disruption that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 1-11, 13-17, 19-23, 25-29, 31-32, 51-52, 57-58, 63-64, 69, 71-83, and 85-86 and 88-89 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) A method of reducing photoaging in a mammal comprising topically administering to the epidermis of the mammal an effective amount of at least one oligonucleotide wherein said oligonucleotide is approximately 2-200 bases in length and wherein the oligonucleotide comprises a phosphodiester backbone; 2) A method of increasing melanin production in epidermal cells, comprising topically administering to said cells, a telomere DNA sequence from the 3' telomere overhang, wherein said DNA sequence is SEQ ID NO: 5 or portion thereof, 3) A method of increasing melanin production in epidermal cells, comprising topically administering to said cells an effective amount of an oligonucleotide sequence, wherein the oligonucleotide sequence is SEQ ID NO: 5, 7, or portion thereof; 4) A method of increasing p53 activity in epidermal cells comprising topically administering an effective amount of DNA fragments to said cells, wherein said fragment is $d(pT)_2$; 5) A method of increasing p53 activity in an epithelial cells comprising directly administering to the cells an effective amount of DNA fragments wherein said fragment is $d(pT)_2$, 6) A method of treating hyperproliferative disease affecting skin cells in a mammal comprising topically administering to the cells an effective amount of DNA fragments, wherein the DNA fragment is SEQ ID NO: 3; 7) A method of inhibiting the proliferation of skin cells in a mammal, comprising topically administering to the skin cells of the mammal an effective amount of DNA fragments that are approximately 2-200 bases in length, the DNA fragments being selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides, and dinucleotides dimers and combinations thereof; 8) A method of inhibiting or reducing DNA damage in epidermal cells, wherein said

DNA damage is caused by UV irradiation, comprising topically administering to the cells of the mammal an effective amount of DNA fragments that are approximately 2-200 bases in length, the DNA fragments being selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides, and dinucleotides dimers and combinations thereof, 9) A method of inhibiting malignant epithelial cells of a mammal, comprising directly administering to the cells of the mammal an effective amount of DNA fragments that are approximately 2-200 bases in length, the DNA fragments being selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides, and dinucleotides dimers and combinations thereof; 10) A method of inhibiting malignant skin cells of a mammal, comprising topically administering to the cells of the mammal an effective amount of DNA fragments that are approximately 2-200 bases in length, the DNA fragments being selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides, and dinucleotides dimers and combinations thereof, and does not reasonably provide enablement for other claimed embodiments embraced by the breadth of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possession of a genus of a mimic of telomere disruption, wherein said mimic comprises at least one oligonucleotide), particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the claimed invention so that it

would operate as intended, e.g. for use in a method of increasing melanin production in epidermal cells.

The state of the art for administering oligonucleotides teaches that relatively little is known about the *in vivo* behavior of oligonucleotide (Plenat, Molecular Medicine, Vol. 1, pp. 250-275) and extrapolation from *in vitro* studies to predict pharmacokinetics and effects in a mammal are difficult and inappropriate (abstract). Furthermore, Plenat teaches that, "oligonucleotides in their natural phosphodiester form are subject to rapid degradation in the blood or intracellular fluid by exonuclease and endonucleases (page 250)." In addition, Plenat teaches that oligonucleotides are inhibited from reaching the target by side effects, which result from interactions with cellular or extracellular proteins as well as complementarity with mRNAs for a protein other than the target (page 252).

Furthermore, the state of the art teaches that the telomere-mimic oligomer (TTAGGG), SEQ ID NO: 11 in the instant application, was well known in the art because Page et al., (Experimental Cell Research, Vol. 252, pp. 41-49, 1999), teach, 5'-TTAGGG-3' (TAG-6) is a hexameric repeat that is added to the 3' ends of chromosomes by telomerase (abstract)." In addition, Ohnuma et al., Anticancer Research, Vol. 17, pp. 2455-2458, 1997, teach that:

> Telomerase is not expressed in normal cells (page 2455). Exceptions to this rule are the presence of telomerase in normal germline cells, adult testis, as well as low levels in bone marrow cells. Practically all immortal cells and malignant tumor cells possess telomerase activity (page 2455).

Furthermore, the state of the art further supports the state of the art by displaying conflicting results using the specific oligomer, e.g. TTAGGG (SEQ ID NO: 11 in instant application) for inhibiting cell proliferation. Ohnuma et al. tested the cell growth inhibitory effects of telomere-mimic oligomer, using TTAGGGn, where n=1, 2, 3 or 4 on 8 human tumor cell lines (abstract).

Ohnuma displays that only the 18-mer (n=3) and the 24-mer (n=4) inhibited cell growth in some of the cell lines and the 6-mer and 12-mer did not displays any cell growth inhibitory effect (page 2457, table 1). However, Page showed that, "TAG-6 can inhibit telomerase activity *in vitro* and this compound was known to have anti-proliferative effects *in vitro* and *in vivo* against a Burkitt's lymphoma cell line and xenographs in nu/nu C57 black mice (page 41)." In addition, Pages teaches that, "cytotoxicity varies among several types cell types tested with specific cells exhibiting a sensitivity not found in two other types of cell lines (page 47)." Thus, the state of the art teaches that oligonucleotide technology is characterized by a high degree of unpredictability.

Furthermore, and with respect to claims directed to gene therapy and directed to any treatment of a mammal; the state of the art in 1998, exemplified by Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998, displays major consideration for any DNA therapy protocol involve issues that include:

> 1) The amount of DNA constructs to be administered,
> 2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;
> 3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and
> 4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method (Anderson, *Nature*, Vol. 392, pp. 25-30, April 1998).

In addition, all of these issues differ dramatically based on the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several

major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

The disclosure provides working examples 1-16 (pages 20-41) a brief description of each example follows.

Examples 1-10 use a dinucleotide pTpT (T2). Examples 1-3 display that using T2 could inhibit different types of cancer cell lines *in vitro*. Examples 4-5 display that using T2 could inhibit different types of normal neonatal cell lines *in vitro*. Example 6 is an *in vivo* comprising topically administering T2 showing that epidermal cell proliferation could be inhibited. Example 7 displays that T2 increases p53 transcription activity in vitro. Example 8 displays that T2 enhances DNA repair via p53 in neonatal human skin cells in vitro. Example 10 displays that T2 induces IL-10 in human keratinocytes, which is likely to cooperate with TNFalpha to inhibit contact hypersensitivity in vitro.

Example 11 uses several different oligonucleotides (SEQ ID NOs: 1, 2, 3, 4, and 6, including T2) and displays that SEQ ID NOs: 1-4 stimulates melanogenesis in human

melanocytes *in vitro*. However, SEQ ID NO: 6 did not stimulate melanogenesis in vitro. Example 12 uses T2 and several oligonucleotides (SEQ ID NOs: 5 and 8-12) and displays that SEQ ID NOs: 5, 8, and 10 were highly melanogenic in vitro, while the reverse complimentary sequence of SEQ ID NO: 11 (SEQ NO: 12) were less active (figure 18). However, SEQ ID NOs: 9 and 10 did not produce significant change in pigment content. Furthermore, Example 12 displays that SEQ ID NO: 1 and T2 can penetrate the skin barrier and produce *in vitro* UV-mimetic effects *in vivo*. In addition, Example 12 displays that oligonucleotide sequence plays a role in determining it melanogenic activity. In addition, Example 12 displays that 5' phosphate is required for efficient uptake.

Example 14 displays that T2 reduced UV-induced mutations *in vivo* and suggest that topical application could be used to lower the mutation rate in carcinogen-exposed skin. Example 15 tested oxidative damage by treating primary newborn fibroblast *in vitro* with T2. The results displayed that T2 increase cell survival. Example 16 tested DNA repair capacity in newborn, young adult, and older adult fibroblast by using either T2 or SEQ ID NO: 1 containing a 5' phosphate. Pre-treatment with oligonucleotides (T2 or SEQ ID NO: 1) resulted in up regulated constitutive of UV-induced proteins (p53, p21, XPA, RPA, ERCC/PF, PCNA). In addition, pre-treatment with oligonucleotides (T2 or SEQ ID NO: 1) increased the removal of photoproducts by 30-60 percent.

With respect to claims 7-19, which are directed to a method of increasing melanin production in epidermal cells comprising contacting said cells with a mimic of telomere disruption or an effective amount of at least one oligonucleotide, wherein the oligonucleotide comprises at least one sequence selected from the group consisting of SEQ ID NOs: 5 and 7 or

portion thereof. The disclosure provides working examples displaying that several oligonucleotide sequences (SEQ ID NOs: 1, 3, 5(7), 6, and 11) stimulate melanogenesis in cells *in vitro* (Examples 11 and 12). Thus, the as-filed specification provides sufficient guidance to display that a telomere DNA sequence from the 3' telomere overhang selected from SEQ ID NOs: 5 or portion thereof (SEQ ID NO: 11) can stimulate pigmentation in cells *in vitro*. However, since the as-filed specification does not provide written support for one skilled in the art to make a genus of mimic of telomere disruption, it would take one skilled in the an undue amount of experimentation to reasonably extrapolate from SEQ ID NO: 5 to any other mimic of telomere disruption. In addition, the specification provides sufficient guidance showing that SEQ ID NOs: 7 (also named SEQ ID NO: 3) and 5 stimulate melanin production in epidermal cells. Furthermore, the unpredictability of using oligonucleotides provided by the art of record is confirmed by the working examples showing neither SEQ ID NOs: 9 or 12 did not produce significant change in pigment content. In addition, the chemical structure of SEQ ID NOs: 9 and 12 are distinct compared to either SEQ ID NOs: 5 or 7. The specification provides sufficient guidance displaying that either SEQ ID NOs: 5, 7(also known as SEQ ID NO: 3), and portion thereof (SEQ ID NO: 11) can stimulate melanin production in epithelial cells.

Furthermore with respect to claim 86, which is directed to a method of preventing or reducing DNA damage in a cell comprising using oligonucleotide therapy comprising an oligonucleotide selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides, and dinucleotides dimers and combinations thereof. The claim reads on reducing DNA damage in a cell, wherein said DNA damage is caused by UV irradiation or DNA damaging chemicals. The specification provides example 16, which displays *in vitro*

culture of fibroblast pre-treated with T2 or SEQ ID NO: 1 and then exposed to UV irradiation resulted in up-regulated and UV-induced levels of several proteins, including the p53 protein. This data displayed that pre-treatment with either T2 or SEQ ID NO: 1 increased removal of photoproducts by 30-60%. Furthermore, Example 14 shows an *in vivo* experiment wherein T2 was applied to an ear of transgenic mice and on the fifth day ears were exposed to UV-B light. The results showed that T2 enhanced DNA repair reduces UV-induced mutations *in vivo* and suggest that topical application could be used to lower the mutation rate in carcinogen-exposed skin. In addition, Example 15 displayed that fibroblast pre-treated with T2 and then exposed to H2O2, where able to survive compared to control cells and complete protection was observed at a low dosage.

Furthermore, in view of the specification and the art of record concerning UV irradiation, it is not apparent what other types of cells other than skin cells would be damaged from exposure to UV irradiation since UV irradiation cannot damage cells under the skin, which would make other cells not accessible to UV irradiation.

Furthermore, with respect to the claimed invention encompassing treating any cell, the as-filed specification does not provide sufficient guidance for one skilled in the art to use any DNA fragment in a method of preventing or reducing DNA damage in any cell other than skin cells because targeting other cells would required different routes of administration such as orally, intravenously, instillation into the bladder, etc., which would expose the DNA fragments to the acidity of the stomach, the host's immune response, the blood stream, which would result in the degradation of the fragments. Thus, the fragments would not reach the target cell at a therapeutic level. In addition, the art of record provides several areas of concerns that are not

address by the as-filed specification. For example, the disclosure lacks sufficient guidance for one skilled in the art to circumvent the problem of degradation of DNA fragments in particularly to oligonucleotides in their natural phosphodiester form particularly since Plenat teaches that, "oligonucleotides in their natural phosphodiester form are subject to rapid degradation in the blood or intracellular fluid by exonuclease and endonucleases (page 250)." In addition, the as-filed specification does not provide sufficient guidance for one skilled in the art to target a specific cell comprising DNA damage with a therapeutic amount of a DNA fragment and more importantly target a particularly pathway in that cell that could use the therapeutic amount of either T2 or SEQ ID NO: 1 for reducing or preventing DNA in the cell since there are numerous pathways in the cell. The as-filed specification only provides sufficient guidance for one skilled in the art to use either T2 or SEQ ID NO: 1 in a method of treating DNA damage in a skin cell by using topically administration because it is not apparent how any route of administration other than topically would target the skin in view of the concerns stated by the art of record.

Furthermore, the art of record teaches that at the time the application was filed *in vivo* administration of oligonucleotides by any route of administration other than direct administration to the cells or topically administering to skin cells so as to produce a therapeutically useful effect was considered by those skilled in the art to be an undeveloped and unpredictable method of treatment, due to the difficulties in delivering therapeutically effective amounts of any given oligo to the correct cellular component of the target cells *in vivo*. For treatment of targeted cancer cells *in vivo*, the chemical structure of the oligos (sequence residues) the length of the oligo, the binding site in the target location in the cell, the chemical composition of the carrier employed to promote cellular uptake, the type of cell targeted, the location of the cell, and the

animal being treated, are critical parameters which determine, whether or not the oligonucleotide therapy as claimed will be successful. Hoke et al. (US Patent No. 5,585,479), provide reasons to support the lack of reasonably correlation between the primary structure of an oligonucleotide to and its activity *in vivo*. More specifically, Hoke discloses that moving the target just one or two bases can greatly reduce, or even eliminate, oligonucleotide activity. Hoke states that, "based upon the above discussions of oligonucleotide activity for oligos that are similar in length and complementary to the same nucleotides, there are no rational explanations or rules that would predict active sequences (column 16, lines 50-54)."

Furthermore, the art of record encompassing the obstacles of nucleic acid therapy by using any naked nucleic acid including oligonucleotides as therapeutic agents, Stull et al., (Pharmaceutical Research, Vol. 12, pg. 476, 1995), which is a review article, discloses that "nucleic acid drugs must overcome several formidable obstacles before they can be widely used as therapeutics", furthermore, "these obstacles require improving the stability of polynucleotides in biological systems, and efficacy of the drug without reducing its selectively may adversely affect the affinity or activity of the reagent."

In addition, in view of the breadth of the term "DNA damage" and the term DNA-damaging chemicals, for example alkylating agents or cross-linking agents, which encompass a broad category of DNA damage with different sites of action, the as-filed specification does not described how the mechanisms of T2 or SEQ ID NO: 1 reasonably correlate to treating a representative number of DNA damage from DNA damaging chemicals and how to use T2 or SEQ ID NO: 1 to reasonably correlates to a genus of DNA damage in any cell caused by DNA-damaging chemical chemicals without an undue amount of experimentation. For example, UV

radiation promotes the formation of a cyclobutyl ring between adjacent thymine residues on the same DNA strand to form an intrastrand thymine dimer and alkylating agents is correlated with deficient repair of 0^6-alkylguanine lesions (See Voet and Voet, John Wiley and Sons, pages 967-972). In view of the art record, DNA damage can be caused by distinct mechanisms and the as-filed specification does not provide sufficient guidance for one skilled in the art to reasonably extrapolate from using T2 or SEQ ID NO: 1 for reducing DNA damage from UV irradiation in skin cells to using any other DNA fragment for reducing DNA damage because the art of record teaching the unpredictability of using distinct oligonucleotides for any method in the claimed invention. Furthermore, the specification only provides sufficient guidance for one skilled in the art to make and/or use several distinct oligonucleotide sequence for increasing melanin production and therefore, it would take one skilled in the art an undue amount of experimentation to reasonably correlate the results observed when using several different DNA fragments, including T2 and SEQ ID NO: 1 for increasing melanin production in skin cells to using any DNA fragment in a method of inhibiting or reducing DNA damage in any cell, wherein said DNA damage is caused by a chemical agent because of the concerns provided by the art of record.

Furthermore, the concerns set forth above are further confirmed by the review article by Branch (TIBS, Vol. 23, pp. 45-50, 1998), Branch states that:

> "Non-antisense molecule effects are not the only impediments to rational antisense drug design. The internal structure of target RNAs and their association with cellular proteins create physical barriers' (page 45);
> "The challenge is to identify antisense molecules that are complementary to vulnerable sites in target RNAs. This is hard to do. RNAs are complex molecules with intricate structures" (page 49);
> "Since accessibility cannot be predicted, rational design of antisense molecules is not possible" (page 49); and

> "It is not clear whether *in vitro* screening techniques of the sort used by Milner and co-workers will identify ODNs that are effective *in vivo* techniques, straightforward new screening techniques need to be developed for use in cells" (page 49)

Thus, one skilled in the art attempting to practice the claimed invention would first look to the as-filed specification for guidance as to which of the DNA fragments to use as therapeutic nucleic acids for treating any cell including epithelial cells. However, the art of record indicates that determination of DNA sequences effective for use in any therapeutic method remains unpredictable. Furthermore, determining an effective fragment and transferring the fragment to an adequate number of cells *in vivo* and getting specific binding between the fragment and the target location in an amount sufficient to produce a therapeutic effect in any mammal remain unpredictable at the time the invention was made (See Stull et al.; Branch; Hoke et al.; Anderson, Verma; Ohnuma, Plenat, and Page). The art of record indicated that several obstacles must be overcome before DNA fragments are employed in any therapeutic method in any mammal including humans. In addition, the as-filed specification uses epithelial cells *in vitro* or topically administering fragments to skin cells and it would take one skilled in the art an undue amount of experimentation to reasonably correlate from skin cells to any other cells *in vivo* because each type of cell functions as an individual entity and possesses different cellular mechanisms responding to a variety of different environmental cues, which can not be duplicated *in vitro*. Therefore, the as-filed specification fails to address any of these issues, which would therefore lead one skilled in the art to believe that *in vivo* administration of any of the disclosed DNA fragments for use in any cells other than skin cells so as to generate a therapeutic effect would be unpredictable.

Therefore, in view of the breadth of claim 86, the unpredictability of oligonucleotide therapy provided by the art of record, and the lack of guidance provided by the as-filed specification for the broad DNA fragments, and because the claim encompasses a broad range of DNA damage and the as-filed specification only provides sufficient guidance for one skilled in the art to make and/or use an oligonucleotide in a method of inhibiting or reducing DNA damage in a skin cell, wherein said damage is caused by UV irradiation, comprising topically administering to the cells of the mammal an effective amount of DNA fragments that are approximately 2-200 bases in length, the DNA fragments being selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides, and dinucleotides dimers and combinations thereof.

In addition, with respect to claims 71-74, which are directed to a method of increasing p53 activity in a cell using a DNA fragment selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides, and dinucleotides dimers and combinations thereof. The specification states that, "GADD45 and SD1 genes are known to be transcriptionally regulated by the tumor suppressor protein p53." Example 7 displays an *in vitro* assay showing that intranuclear p53 was detected in T2 treated cells, which is consistent with the induction of p53 regulated listed above in cells by T2. That specification states that, "T2 increases the transcriptional activity of p53." Example 9 is an *in vitro* assay that shows that enhanced repair of BP-DNA addicts by T2 requires p53. Also in example 12, the disclosure displays that SEQ ID NO: 1 and 6 activate p53 and inhibit cell proliferation similar to T2. The specification demonstrates that T2 is affective to increase p53 in cancer cells *in vitro*. In view of the guidance provided by the disclosure and the breadth of the claims, it would require an undue

amount of experimentation for one skilled in the art to reasonably extrapolate that a therapeutic effect would be observed *in vivo* in any cell other than epithelial cell because of the concerns stated by the art of record. In addition, the art of record further states that mutant forms of the gene encoding the tumor suppressor p53 are found in numerous human malignancies, but the physiologic function of p53 and the effects of mutations on the function are unknown (IDS, Kern et al. Science, Vol. 256, 1992, pp. 827-830). The as-filed specification contemplates that the fragments are preferably 2-200 bases in length. In addition, the breadth of the phrase "increasing p53 in a cell", the phrase comprises of direct and indirect methods of increasing p53 and the as-filed specification only teaches one skilled in the art how to make and/or use T2 and SEQ NOs: 1 and 6 for use in a method of increasing p53 activity in an epithelial cell by indirect mechanisms. In further support of the state of the art, Jayaraman et al. (IDS, Cell, Vol. 81, 1995, pp. 1021-1029) teach that only very short oligonucleotides were effective to activate p53 in DNA binding assays by directly binding to a region of the p53 C-Terminus. Oligonucleotides up to 40 bases activated binding at a region of the p53 C Terminus, whereas 66-mers or 92-mers actually inhibited binding of p53 (see page 1022, figure 1). Therefore, the as-filed specification lacks sufficient guidance or factual evidence that any size of oligonucleotides larger than 40 bases would be enabled for directly binding to the p53 C-terminus and what nucleotides are essential for the binding to the C-terminus to activate p53 in view of the concerns set forth above by the state of the art (Kern et al. and Jayaraman et al.). Since the art of record teaches that there are numerous ways of increasing p53 in a cell (indirectly or directly) and that the function of p53 and the effects of mutations on the function are unknown and the as-filed specification only teaches or provides factual evidence for how to make and/or use three specific and distinct DNA

fragments, it would take one skilled in the art an undue amount of experimentation to reasonably correlate to any fragment of about 2 to about 200 nucleotides other than the three distinct fragments set forth in the working examples.

Thus, in view of art of record set forth above and the lack of sufficient guidance provided by the as-filed specification it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate to any DNA fragment other than T2 and SEQ NOs: 1 and 6 for use in a method of increasing p53 activity in an epithelial cell comprising directly or topically administering a DNA fragment selected from T2 or SEQ ID NOs: 1 and 6.

Furthermore, with respect to claims 20-25, which are directed to a method of increasing DNA repair in epithelial cells using SEQ ID NOs: 5 or 7. The specification provides example 8, which uses an UV-damaged reporter plasmid to measure the DNA repair capacity of normal cells. The data from the assays displayed that T2 treatment of cells *in vitro* can double the capacity of cells to repair UV-induced DNA damage over 24 hour period. The art of record teaches that DNA repair comprises of a wide variety of pathways (e.g. direct reversal of damage, excision repair, recombinant repair, SOS response). See Voet and Voet, pages 967-972. Furthermore, in view of the specification, which states that, "any epithelial cell is suitable for the method of the claimed invention (page 8)", the specification is not enabled for any route of administration other than direct or topical because of the concerns stated above encompassing route of administration and unpredictability of oligonucleotide therapy. Therefore, in view of the art of record, the as-filed specification is only enabled for a method of increasing DNA repair in skin cells by topically or directly administering T2 to said skin cells and the claimed invention is not enabled for using any other DNA fragment (SEQ ID NO: 5 or 7) in a method for increasing

DNA repair in skin cells because the specification only provides sufficient guidance for one skilled in the art to use several distinct oligonucleotide sequence for increasing melanin production and therefore, it would take one skilled in the art an undue amount of experimentation to reasonably correlate the results observed with T2 to SEQ ID NOs: 5 and 7 because of the art of record set forth above.

Furthermore, with respect to claim 88, which is directed to a method of treating malignant cells of a mammal, comprising contacting said cells with an effective amount of DNA fragments. The specification displays an *in vitro* assay that shows that T2 inhibits cell growth rate in various human carcinoma cells (Examples 1, 2, 3). The disclosure states that, "the response of cancerous cells to T2 is identical to that observed after UV irradiation of these cells and is similar to the response to various antimetabolites that are clinically effective in the treatment of hyperproliferative skin disorders (page 22)." Furthermore in view of the specification, which states that, "any epithelial cell is suitable for the method of the claimed invention (page 8)." As stated above in view of the art of record, the as-filed specification is only enabled for treating skin cells by topically to said skin cells or directly administering DNA fragments selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides, and dinucleotides dimers and combinations thereof to epithelial cells because other routes of administration such as orally, intravenously, instillation into the bladder, etc. would expose the fragments to the acidity of the stomach, the host's immune response, the blood stream, which would result in the degradation of the fragments and the fragments would not reach the target cell at a therapeutic level. Therefore, the claimed invention is only enabled for a method of inhibiting malignant cells of a mammal, comprising topically

administering to skin cells or directly administering to the epithelial cells of the mammal an effective amount of DNA fragments that are approximately 2-200 bases in length, the DNA fragments being selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides, and dinucleotides dimers and combinations thereof.

In addition, claims 26-29 and 31-32 are directed to a method of inhibiting proliferation of epithelial cells using SEQ ID NO: 5 or 7 and claims 85 and 89 are directed to a method of inhibiting proliferation of skin cells in a mammal using topical administration of any DNA fragment selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides, and dinucleotides dimers and combinations thereof. The specification displays *in vitro* assays showing inhibition of normal human neonatal keratinocyte or fibroblast cells (Examples 4 and 5). In addition, the guinea pigs received topical applications of T2 for three days and on the fourth day punch biopsies were taken and the results displayed inhibition of the cells isolated from the pigs (Example 6). Claims 26-29 and 21-32 of the instant application require contacting a cell or administrating DNA fragments to epithelial cells. The as-filed specification does not enable one skilled in the art to contact a cell or administer to epithelial cells the DNA fragments as claimed, except when administered topically to the epidermis as contemplated by claim 85 or directly to the epithelial cells. The state of the art for oligonucleotide therapy is considered unpredictable as set forth above. The disclosure demonstrates *in vitro* data, however, the disclosure does not teach one skilled in the art how to use a DNA fragments in any route of administration other than topically or directly. For example other routes of administration such as orally, intravenously, instillation into the bladder, etc. would expose the fragments to the acidity of the stomach, the host's immune response, the

blood stream, which would result in the degradation of the fragments and the fragments would not reach the target cell at a therapeutic level. Thus, in view of the specification and the art of record, claims 26-32, 85, and 89 are only enabled for a method of inhibiting proliferation of epidermis epithelial cells comprising topically administering or directly administering to said cells an effective amount of DNA fragments selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides, and dinucleotides dimers and combinations thereof.

In addition, with respect to claim 76, wherein the claim encompasses using DNA fragment comprising SEQ ID NOs: 1, 2, 3, or 4 and combinations thereof, which are ultraviolet-irradiated in a method of treating hyperproliferative disease affecting epithelial cells, the as-filed specification and the state of the art do nor provide sufficient guidance for one skilled in the art to make and use ultraviolet irradiated SEQ ID NOs: 1, 2, 3, or 4 because ultraviolet irradiation results in photodimerization between two adjacent pyrimidine residues (T or C present in DNA fragments or dinucleotides (US Patent No. 5,955,059, column 3) and SEQ ID NOs: 1-4 do not have two adjacent pyrimidine residues next to each other. Thus, the oligonucleotide sequences are not enabled to form dimers because of the reason listed above, therefore claim 76 is not enabled by the as-filed specification.

As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed DNA fragments generates a therapeutic effect, how is it apparent as to how one skilled in the art, without any undue experimentation, practices any nucleic acid therapy method as contemplated by the claims, particularly given the

unpredictability of nucleic acid therapy as a whole and/or the doubts expressed in the art of record.

In view of the In re Wands Factors, the claimed invention is only enabled for: 1) A method of reducing photoaging in a mammal comprising topically administering to the epidermis of the mammal an effective amount of at least one oligonucleotide wherein said oligonucleotide is approximately 2-200 bases in length and wherein the oligonucleotide comprises a phosphodiester backbone; 2) A method of increasing melanin production in epidermal cells, comprising topically administering to said cells, a telomere DNA sequence from the 3' telomere overhang, wherein said DNA sequence is SEQ ID NO: 5 or portion thereof, 3) A method of increasing melanin production in epidermal cells, comprising topically administering to said cells an effective amount of an oligonucleotide sequence, wherein the oligonucleotide sequence is SEQ ID NO: 5, 7, or portion thereof; 4) A method of increasing p53 activity in epidermal cells comprising topically administering an effective amount of DNA fragments to said cells, wherein said fragment is $d(pT)_2$; 5) A method of increasing p53 activity in an epithelial cells comprising directly administering to the cells an effective amount of DNA fragments wherein said fragment is $d(pT)_2$, 6) A method of treating hyperproliferative disease affecting skin cells in a mammal comprising topically administering to the cells an effective amount of DNA fragments, wherein the DNA fragment is SEQ ID NO: 3; 7) A method of inhibiting the proliferation of skin cells in a mammal, comprising topically administering to the skin cells of the mammal an effective amount of DNA fragments that are approximately 2-200 bases in length, the DNA fragments being selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides, and dinucleotides dimers and combinations thereof; 8) A method of inhibiting or

reducing DNA damage in epidermal cells, wherein said DNA damage is caused by UV irradiation, comprising topically administering to the cells of the mammal an effective amount of DNA fragments that are approximately 2-200 bases in length, the DNA fragments being selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides, and dinucleotides dimers and combinations thereof, 9) A method of inhibiting malignant epithelial cells of a mammal, comprising directly administering to the cells of the mammal an effective amount of DNA fragments that are approximately 2-200 bases in length, the DNA fragments being selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides, and dinucleotides dimers and combinations thereof; 10) A method of inhibiting malignant skin cells of a mammal, comprising topically administering to the cells of the mammal an effective amount of DNA fragments that are approximately 2-200 bases in length, the DNA fragments being selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides, and dinucleotides dimers and combinations thereof.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable the for 1-10 listed above. Given that oligonucleotide therapy wherein any DNA fragment is employed to correct a disease or a medical condition in any mammal was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a oligonucleotide therapy effect produced by any DNA fragment cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of oligonucleotide therapy. Thus, oligonucleotide therapy was considered unpredictable at the time the invention was made.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 4 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites the limitation "the polynucleotide" in line 13, page 42. There is insufficient antecedent basis for this limitation in the claim.

Claim 13 recites the limitation "the inhibitor" in line 10, page 43. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

SEQ ID NOs: 5 and 11 only enjoys priority to 3/31/00 because absence to evidence to the contrary, the examiner reviewed all prior applications and noted that SEQ ID NOs: 5 and 11 were not provided in any of the CIP applications.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C.

122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 51-52 are rejected under 35 U.S.C. 102(a) as being anticipated by Shay et al. (US Patent No. 6,015,710). Shay teaches a pharmaceutical composition comprising the oligonucleotide 5'-GTTAGGGTAG-3' [SEQ ID NO: 9] (column 53, claim 2). This oligonucleotide sequence is 100% identical to SEQ ID NO: 5 in the instant application.

Claims 51-52 are rejected under 35 U.S.C. 102(e) as being anticipated by Shay et al. (US Patent No. 6,046,307). Shay teaches a pharmaceutical composition comprising the oligonucleotide 5'-GTTAGGGTTAG-3' [SEQ ID NO: 13] (column 12, lines 4-21 and column 72, claim 11). This oligonucleotide sequence is 100% identical to SEQ ID NO: 5 in the instant application.

Claim 85 is rejected under 35 U.S.C. 102(e) as being anticipated by Beer-Romero et al (US Patent No. 5,858,987). Beer-Romero teaches a method of inhibiting proliferation of a cells expressing p53 comprising administering to an animal, by topical application to said cells, an E6AP antisense construct in an amount sufficient to produce in said cells a population of antisense nucleic acids which specifically hybridize to mRNA transcribed by a gene encoding an E6 associated protein under physiological conditions, which antisense nucleic acids inhibit expression of said E6AP gene inhibit proliferation of said cells, wherein said cells is an epithelial cell, (column 33, claims 36, 37, 39).

Claim 88 is rejected under 35 U.S.C. 102(e) as being anticipated by Iversen et al (IDS, US Patent No. 5,643,890). Iversen teaches a method of inhibiting proliferation of immortal cells

or cells that express telomerase by directly injecting into the tumor a single telomere motif, SEQ ID NO: 3 (column 14, Example 7).

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-2742.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635
3/11/02

DAVE T. NGUYEN
PRIMARY EXAMINER